REMARKS

Applicants respectfully request reconsideration of the present application in view of the following commentary.

I. Status of the Claims

No claim amendments are made in this response. Claims 1-27, 37-38, 41, 44-50 and 61-63 were previously cancelled. Claims 28-36, 39-40, 42-43, 51-60 and 64-72 are pending.

II. Rejection of Claims under 35 U.S.C. §103(a)

A. Liversidge and Radhakrishnan

Claims 28-36, 39-40, 51-60 and 64-72 are rejected under 35 U.S.C. §103(a) for allegedly being obvious over U.S. Patent No. 5,145,684 to Liversidge et al. ("Liversidge") in view of U.S. Patent No. 5,049,389 to Radhakrishnan ("Radhakrishnan"). Office Action, at pages 3-7. Applicants respectfully traverse the rejection.

The rejection rationale set forth in the Office Action is unclear and inconsistent. For the ease of discussion, the Examiner's positions are summarized below:

(i) The Examiner asserts that Liversidge teaches nanoparticles of a crystalline drug and Radhakrishnan teaches BECOTIDE, an aqueous suspension of beclomethasone dipropinate. *See* Office Action, at pages 4-5. The Examiner appears to contend that the claimed invention is obvious over the teaching of the primary reference, Liversidge, which discloses the genus of crystalline drugs, in view of the teaching of secondary reference, Radhakrishnan, which discloses the species of beclomethasone.

(ii) The Examiner also asserts that Radhakrishnan's deficiencies in teaching a nanoparticulate size of crystalline beclomethasone particles and a surface stabilizer adsorbed on the surface of beclomethasone particles are cured by Liversidge. *See* Office Action, page 6, first

full paragraph. The Examiner appears to apply an "obvious to try" rationale, i.e., it would have been obvious for one skilled in the art to modify BECOTIDE® disclosed by Radhakrishnan and try to obtain a stable nanoparticulate beclomethasone composition in view of the teaching of Liversidge.

(iii) The Examiner's characterization of Radhakrishnam is in error. The particle size in Radhakrishnan refers to a micelle structure and one of ordinary skill in the art would not associate the size of a micellular structure with size characterization of a particulate drug.

Each possible ground of rejection is addressed below.

(i) Genus v. Species

Pursuant to MPEP 2144.08, to reject claims directed to a species or a subgenus in view of prior-art teaching of the genus, the Examiner is required to articulate why one skilled in the art would have a reason to select the claimed species or subgenus.

Liversidge discloses over 40 categories of active agents. The Examiner's rejection improperly disregards the guideline set forth in MPEP 2144.08 concerning an obviousness rejection of a species in view of a prior-art disclosure of a genus. More specifically, the Examiner fails to establish that one skilled in the art would have any reason to select the subgenus encompassing the species of beclomethasone, let alone the species itself. Rather, the Examiner made a logic leap, with the aid of improper hindsight, by citing the secondary reference, Radhakrishnan, which merely discloses a commercial BECOTIDE® formulation without any disclosure as to how to reduce beclomethasone particle size to obtain a stable nanoparticulate beclomethasone composition. Therefore, one skilled in the art would not have had any reason to select the species of beclomethasone based on the teachings of the cited references.

This point has been affirmed by *Takeda Chemical Industries v. Alphapharm Pty.*, 492 F.3d 1350 (Fed. Cir. 2007). In *Takeda*, the prior art discloses "hundreds of millions of TZD compounds" and specifically identifies fifty-four compounds, including compound b. The court found non-obvious to select compound b, however, because there was no indication in the prior art to show that compound b fell in the group of "the best performing compounds." *Id.*, at 1357.

(ii) Obvious to Try

The Examination Guidelines for Determining Obviousness under 35 U.S.C. § 103 in view of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* ("the Guidelines") requires the Examiner to articulate the following:

(1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;

(2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;

(3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The Examiner's obviousness rejection under Section 103(a) fails to articulate a reasonable expectation of success. Specifically, Liversidge expressly states that not every combination of active agent and surface stabilizer can produce a stable nanoparticulate active agent composition (column 7, lines 21-23; comparative examples A-F).

(iii) Radhakrishnan's teaching of particle size

Radhakrishnan fails to disclose a nanoparticulate beclomethasone composition having an effective average particle size of less than 1000 nm of the crystalline beclomethasone particles as

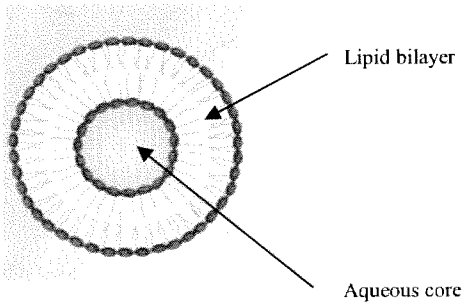
prescribed by the present claims. The Examiner relies on Figure 4 and col. 16, line 53 through col. 17, line 17 of Radhakrishnan for the alleged teaching of particle size of BECOTIDE®.

Radhakrishnan explicitly discloses that the liquid aerosol particle size of BECOTIDE® is 2 μm. Column 16, lines 61-64. Radhakrishnan further compares the particle size of BECOTIDE® with liposome-contained beclomethasone, the latter having a particle size of 0.4 μm. Column 16, line 66, through column 17, line 2.

As one skilled in the art would have understood, the particle size disclosed by Radhakrishnan is not comparable to the particle size of crystalline beclomethasone particles of the claimed invention.

First, Radhakrishnan's aerosol particle size represents the size of aerosol droplet rather than the size of the crystalline beclomethasone particles. *See* column 15, lines 60-61.

Second, liposome acting as a drug delivery vehicle is well known in the field. The structure of a liposome is depicted in the diagram below. To function as a drug delivery vehicle, liposome dissolves the water-soluble drug in the aqueous core or solubilizes poorly water-soluble drugs in the lipid bilayer.



Radhakrishnan's invention relates to employing modified liposomes having high cholesterol content to deliver beclomethasone. *See* column 11, lines 4-12. The beclomethasone is ***solubilized*** in the cholesterol to achieve the small particle size of the aerosol droplets. *See*

column 11, lines 43-45. Accordingly, Radhakrishnan fails to disclosed the particle size of solid, crystalline beclomethasone particles of the claimed invention.

In view of the foregoing, Applicants respectfully request withdrawal of the rejection.

B. Liversidge, Radhakrishnan and Spear

Claims 42-43 are rejected under 35 U.S.C. §103(a) for allegedly being obvious over Livesidge in view of Radhakrishnan, and further in view of U.S. Patent No. 5,525,623 to Spear et al. ("Spear"). Office Action, at pages 9-11. Applicants respectfully traverse the rejection.

Spear is cited for the alleged teachings of jet nebulizers and ultrasonic nebulizers (Office Action, page 10, second full paragraph) but fails to compensate for the deficiencies of Liversidge and Radhakrishnan. Moreover, claims 42-43 depend from a non-obvious base claim as discussed above, and therefore, are also non-obvious. Withdrawal of the rejection is warranted.

III. Provisional Double Patenting Rejection

Claims 28-33, 39-40, 51-60, 66, 69 and 72 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-7, 9-11 and 13-14 of copending Application No. 10/035,324 in view of Liversidge and Radhakrishnan. Claims 28-33, 53-60, 66, 69 and 72 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 60-61, 64-65, 69-70 and 72-76 of copending Application No. 10/768,194 in view of Liversidge and Radhakrishnan. Finally, claims 28-36 and 51-60 are rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-11 and 17-18 of copending Application No. 12/292,092 in view of Liversidge and Radhakrishnan. Applicants respectfully traverse each ground of the rejection.

The allegedly conflicting claims are in applications which were filed after the present application. According to MPEP 804, the Examiner should allow the earlier filed application to

issue without filing a terminal disclaimer. The relevant MPEP sections are excerpted below, with emphasis added:

> *If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds,* ***the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer...***
>
> *If "provisional" ODP rejections in two applications are the only rejections remaining in those applications,* ***the examiner should withdraw the ODP rejection in the earlier filed application thereby permitting that application to issue without need of a terminal disclaimer...***

Accordingly, Applicants respectfully request withdrawal of the provisional double patenting rejections.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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By _____

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